RLL-170US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: RAMPAL *et al.*

Application No.: 09/941,970

Filing Date: August 29, 2001

Examiner: Micah Paul Young

Group Art Unit: 1615

Title: **CONTROLLED RELEASE FORMULATION OF ERYTHROMYCIN OR A DERIVATIVE THEREOF**

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I hereby certify that this correspondence is being facsimile transmitted on December 19, 2003 to the United States Patent and Trademark Office.

Kim Campbell

Kim Campbell

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION DATED AUGUST 19, 2003

In view of the following remarks, reconsideration and allowance of this application are requested. Claims 1, 2, and 5-12 are pending with claims 1, 11, and 12 being independent.

Claim 1 is directed to a controlled release formulation of erythromycin A or a derivative thereof and pharmaceutically acceptable rate controlling polymers that is suitable for once daily administration. The formulation includes erythromycin from about 66% w/w to about 90% w/w of the total tablet weight and pharmaceutically acceptable rate controlling polymers from 0.1% w/w to about 4% w/w of the total tablet weight.

Claims 1, 2, and 5-12 have been rejected as being obvious over Talwar et al (WO 00/15198) in view of Fuisz et al (U.S. Patent No. 5,518,730), Ayer et al (U.S. Patent No. 6,096,339) and Misra et al (U.S. Patent No. 5,869,098).

Talwar discloses a controlled release dosage form that includes an active ingredient, a gas generating component, a swelling agent, a viscolyzing agent, and gelling polymers and provides a combination of temporal and spatial (e.g., particular portion of the gastrointestinal tract) control over drug delivery. Talwar discloses examples of formulations that include as the active ingredient one of either ciprofloxacin, acyclovir, diltiazem, ranitidine, or captopril. The active ingredient is present in the formulations at percentages of between 37.88% (Example 17) and 88 % (Table 22) w/w of the tablet.

Although Talwar does not specifically define his polymers (i.e., a gas generating component, a swelling agent, a viscolyzing agent, and gelling polymers) as rate controlling polymers, Talwar's description discloses these polymers to be rate controlling polymers. These rate controlling polymers are present in Talwar's formulations at percentages of between approximately 8% (Table 21) and 50% (Example 6, Table 11) w/w of the tablet. As such Talwar does not describe or suggest a controlled release formulation that includes: (1) between about 0.1% w/w to about 4% w/w of rate controlling polymers; or (2) between about 66% w/w to about 90% w/w of erythromycin A or a derivative, as recited in claim 1.

Talwar characterizes his formulations as providing a combination of temporal and spatial control of the drug delivery by means of the combination of a gas generating component, a swelling agent, a viscolyzing agent, and, optionally, a gel forming agent, collectively termed a "Controlled Gas Powered System." See Abstract and Col. 4, lines 38-41. Talwar also states that hydrophilic water-soluble polymers can be used in the formulations to modify the rate of release of the drug from the composition. See Col. 10,

lines 1-14. Talwar's gas generating component, swelling agent, viscolyzing agent, gel forming agent, and hydrophilic water-swellable polymers function as rate controlling polymers which, taken together, make up between 8% and 50% of the tablet by weight.

Again, Talwar does not use the claim term "rate controlling polymer" but nonetheless many of the polymers disclosed in Talwar are rate controlling polymers. For example, the gas generating component, the swelling agent, and the viscolyzing agent combine to cause the dosage form to swell to twice its volume. The swelling prevents the passage of the drug through the pylorus, thereby extending the time that the dosage form is in and the drug is delivered to the gastrointestinal tract. See Col. 3, lines 30-43. Talwar gives as examples of swelling agents: cross-linked polyvinylpyrrolidone, cross-linked carboxy methylcellulose sodium, cross-linked carboxy methylcellulose, and sodium starch glycolate. See Col. 8, lines 16-36.

The gel forming polymer produces a cross-linked three-dimensional molecular network that is retained in the stomach and releases the drug over a sustained period of time. See Col. 4, lines 42-64. The gel forming agent cross-links to form a stable matrix structure such that the matrix structure is retained in the stomach for an extended time. The viscolyzing agent viscolyzes when it contacts the gastrointestinal fluids. Talwar gives as examples of viscolyzing agents carbohydrate gums including xanthan gum, tragacanth gum, gum karaya, guar gum, and acacia. See Col. 8, lines 37-55. Moreover, Talwar states that "the viscolyzing agent and gel forming polymer provide a tortuous diffusion pathway for the drug, thereby resulting in controlled drug release." See Col. 9, lines 30-41. Talwar gives as examples of gel forming polymers alkali metal salts of alginic acid, alkali metal salts of pectic acid, the water soluble salt of polyuronic acid, sodium alginate, potassium alginate, and ammonium alginate. See Col. 9, lines 40-52.

Talwar also describes the use of hydrophilic water-soluble polymers in his compositions as useful for modifying the rate of release of the drug from the composition. As examples, Talwar gives hydroxylpropyl methylcellulose, hydroxypropylcellulose, and polyacrylic acid (e.g., Carbopol). See Col. 10, lines 1-14.

Talwar's examples further illustrate his use of rate controlling polymers at between 8% (Table 21) and 50% (Example 6, Table 11) w/w of the tablet. For example, the rate controlling polymers of Example 1 are xanthan gum, sodium alginate, cross-linked carboxymethylcellulose, and cross-linked polyacrylic acid (Carbopol), which together make up greater than 14% of the tablet weight. The rate controlling polymers of Example 2 are xanthan gum, sodium alginate, and cross-linked polyvinylpyrrolidone, which together make up greater than 17% of the tablet weight. The rate controlling polymers of Example 3 are xanthan gum, sodium alginate, and cross-linked carboxymethylcellulose, which together make up greater than 9% of the tablet weight. The rate controlling polymers of Example 4 are xanthan gum, sodium alginate, and cross-linked polyvinylpyrrolidone, which together make up greater than 18% of the tablet weight. The remaining examples variously use as rate controlling polymers one or more of xanthan gum, sodium alginate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, and cross-linked polyacrylic acid at total amounts ranging from greater than 8% to greater than 50%.

Talwar notes that the Controlled Gas Powered System is retained for longer periods of time in the stomach than many other dosage forms and, consequently, the drug is released at a constant and controlled rate. See Col. 5, lines 1-12. Thus, even though Talwar does not use the term "rate controlling polymer," Talwar's polymers are rate controlling polymers and many of Talwar's polymers directly correspond to the various rate controlling polymers recited in claims 5-10 of the instant application.

Neither Fuisz, Ayer, nor Misra, taken separately or in combination with Talwar, cure Talwar's failure to describe or suggest rate controlling polymers making up from 0.1% w/w to about 4% w/w of the total tablet weight. For example, Fuisz discloses using rate controlling polymers at between 50% and 99% w/w of the tablet. See Col. 11, lines 15-52 and Table 1. Ayer discloses using rate controlling polymers at between approximately 17% and 30% w/w/ of the tablet. See Col. 6, lines 17-38, and col. 8, lines, 24-46. Misra discloses using a coating of hydroxypropyl cellulose or hydroxypropyl methyl cellulose, but does not disclose the amount used. See Examples I-VI. Based on these disclosures, one of skill in the art reading Talwar, Fuisz, Ayer, and Misra, separately or in combination, would have found no description or suggestion for reducing the amount of rate controlling polymer to between 0.1% and 4% w/w/ of the tablet, as recited in claim 1.

As such, Applicants submit that none of the cited references, take separately or in combination, describe or suggest rate controlling polymers making up from 0.1% w/w to about 4% w/w of the total tablet weight and, for at least this reason, independent claim 1 and dependent claims 2 and 5-10 are allowable over Talwar, Fuisz, Ayer, and Misra, taken separately or in combination.

With respect to the amount of erythromycin, neither Talwar, Fuisz, Ayer, nor Misra describes or suggests a controlled release formulation that contains between about 66% w/w to about 90% w/w of erythromycin A or a derivative. As recognized by the Office Action, Talwar does not disclose any examples with erythromycin or clarithromycin as the pharmaceutically active agent, nor does it specify at what level potential substitutes would be formulated. Instead, Talwar merely lists illustrative drugs "that are suitable for the present invention" and includes clarithromycin in the list. See Col. 7, lines 12-38.

The Office Action states that "substituting and interchanging these compounds is within the level of ordinary skill in the art." Assuming for the sake of argument that it would have been within the level of ordinary skill in the art to interchange clarithromycin and ciprofloxacin, the cited references fail to describe or suggest at what dosage strength the clarithromycin would be interchanged. The chemical arts is an unpredictable field and there is no basis upon which one can simply assert that one can interchange compounds, broadly classed as antibiotics, at the same level within a formulation. Each compound has unique physical properties, such as dissolution profile, spatial bioavailability, and adsorption within the gastrointestinal tract. All of these properties affect the amount or concentration level necessary to impart the intended therapeutic effect of the formulation. As a consequence, Applicants submit that there is no general rule that antibiotics can be substituted in formulations without regard to the formulation or the level of the antibiotic, as apparently asserted by the Office Action.

Specifically, Talwar lacks any description or suggestion of the concentration ranges for which such a substitution of active ingredients would be expected to be successful. Talwar's examples illustrate various active ingredients, of which each contains a varying concentration level of the active ingredient (e.g., from between 37.88% (Example 17) to 88 % (Table 22) w/w of the tablet). Further, Talwar states that the amount of drug "typically ranges from about 0.5 mg up to about 1200 mg", which gives no guidance on the level of clarithromycin to use in place of the various active ingredients disclosed. Even within the group of examples in which Talwar discloses ciprofloxacin, there are varying concentration levels of the active ingredient, namely, approximately 52% (Example 10) to approximately 88% (Table 22).

This lack of teaching or guidance by Talwar would not have sufficiently described or suggested to one skilled in the art that ciproflaxocin and clarithromycin can be interchanged at the same dosage strength and in the same formulation. Applicants submit

that only with the present disclosure in hand would one skilled in the art have been motivated to substitute clarithromycin for ciprofloxacin at the same concentration level and in the same formulation as disclosed in Talwar.

Further, neither Fuisz, Ayer, nor Misra, taken separately or in combination with Talwar, cure Talwar's failure to describe or suggest a controlled release formulation that contains between about 66% w/w to about 90% w/w of erythromycin A or a derivative.

Fuisz discloses a controlled release formulation and lists erythromycin as one of more than one hundred other individual bio-active agents. See Col. 7, line 65 through Col. 9, line 8. Assuming for the sake of argument that there would have been some description or suggestion within Fuisz to substitute clarithromycin for ciprofloxacin, there still would have been no description or suggestion to substitute clarithromycin at the same level as the ciprofloxacin disclosed in Talwar. The only disclosure in Fuisz that references an erythromycin derivative is Example 1, in which 200 mg of vancomycin is melt spun into a polymer product and makes up 11% of the product. See Col. 12, lines 51-67 and Table 1. Thus, at most, Fuisz would have motivated one of skill in the art to make a formulation that includes 11% clarithromycin rather than the claimed 66% to about 90% w/w.

Ayers discloses a controlled release formulation in which 500 mg of ciprofloxacin is described as a potential bio-effective agent for incorporation in a tablet. See Example 4. Ayers also states that a large number of active ingredients, including erythromycin, can be used in the dosage form. See Col. 11, line 48 through Col. 12, line 36. Ayers thus discloses that erythromycin can be used in his tablets without disclosing the amount of erythromycin to use. Again, assuming for the sake of argument that there would have been some description or suggestion within Ayer to substitute erythromycin for

ciprofloxacin, there would still have been no description or suggestion to substitute erythromycin for ciprofloxacin at the same level as the ciprofloxacin disclosed in Talwar.

Misra discloses a fast dissolving comestible formulation that can include a bio-active agent selected from more than seventy five different classes of drugs as well as from numerous specific drugs, including clarithromycin and ciprofloxacin. See Col. 8, line 53 through Col. 10, line 29; and Col.12, lines 35-38. However, the amount of clarithromycin or ciprofloxacin to use is not disclosed. The Office Action asserts that it would have been obvious for one of skill in the art to have modified Talwar in view of Misra to include Misra's clarithromycin. Again, neither Talwar nor Misra has a description of suggestion that clarithromycin can be substituted for ciprofloxacin at the claimed levels.

Accordingly, for at least this additional reason, independent claim 1 and dependent claims 2 and 5-10 are allowable over Talwar, Fuisz, Ayer, and Misra, taken separately or in combination.

Independent claim 11 is directed to a monolithic controlled release formulation with 1000 mg of clarithromycin. Like claim 1, there is no description of suggestion in the art of record that clarithromycin could have been substituted for ciprofloxacin without regard to the quantity of ciprofloxacin disclosed. As such, claim 11 is allowable over the art of record for the same reasons that claim 1 is allowable.

Independent Claim 12 is directed to a process for making a controlled release dosage form of erythromycin A or a derivative. Like the dosage form of claim 1, the dosage form of claim 12 includes the erythromycin or derivative being present in an amount from about 66% w/w to about 90% w/w of the total tablet weight and one or more rate controlling polymers making up from about 0.1% to about 4% w/w of the

tablet. As such, claim 12 is allowable over the art of record for the same reasons that claim 1 is allowable.

Conclusion

For the reasons stated above, the Examiner is urged to allow claims 1, 2, and 5-12. Authorization is hereby given to charge any fees deemed to be due in connection with this Response to Office Action to Deposit Account No. 50-0912.

Respectfully submitted,

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Date: December 19, 2003

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DATE: 19 December 2003 #OF PAGES: (INCLUDING THIS COVER)

TO: Micah-Paul Young/ USPTO
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FROM: Kim Campbell, IP Dept.

RE: U.S. Patent Application No. 09/941,970
Title: CONTROLLED RELEASE FORMULATION OF ERYTHROMYCIN OR A DERIVATIVE THEREOF
Our Ref. No.: RLL-170US

Dear Mr. Young:

Attached please find the response to Office Action regarding the above matter.

If you have any questions please contact William Hare at 609-720-5378.

Thank you,

Kim Campbell
Patent Legal Assistant

Attachment